

Attachment 1

Coly-Mycin® M Parenteral

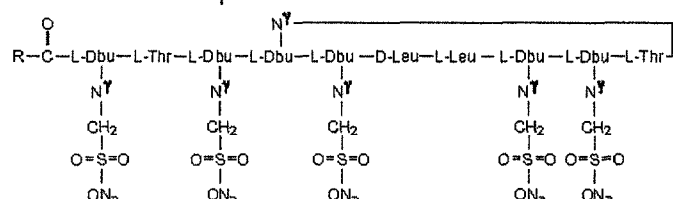
(Colistimethate for Injection, USP)

FOR INTRAMUSCULAR AND INTRAVENOUS USE

DESCRIPTION

Coly-Mycin® M Parenteral (Colistimethate for Injection, USP) is a sterile parenteral antibiotic product which, when reconstituted (see **Reconstitution**), is suitable for intramuscular or intravenous administration.

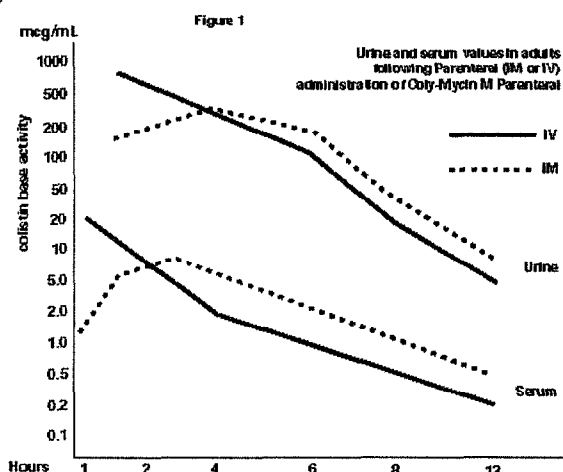
Each vial contains colistimethate sodium or pentasodium colistinmethanesulfonate (150 mg colistin base activity). Colistimethate sodium is a polypeptide antibiotic with an approximate molecular weight of 1750. The empirical formula is $C_{58}H_{105}N_{16}Na_5O_{28}S_5$ and the structural formula is represented below:



Dbu is 2,4-diaminobutanoic acid; R is 5-methylheptyl in colistin A and 5-methylhexyl in colistin B

CLINICAL PHARMACOLOGY

Typical serum and urine levels following a single 150 mg dose of Coly-Mycin M Parenteral IM or IV in normal adult subjects are shown in Figure 1.



Higher serum levels were obtained at 10 minutes following IV administration. Serum concentration declined with a half-life of 2–3 hours following either intravenous or intramuscular administration in adults and in the pediatric population, including premature infants.

Average urine levels ranged from about 270 mcg/mL at 2 hours to about 15 mcg/mL at 8 hours after intravenous administration and from 200 to about 25 mcg/mL during a similar period following intramuscular administration.

Microbiology: Colistimethate sodium is a surface active agent which penetrates into and disrupts the bacterial cell membrane. It has been shown to have bactericidal activity against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-negative microorganisms: *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Susceptibility Tests: Colistimethate sodium is no longer listed as an antimicrobial for routine testing and reporting by clinical microbiology laboratories.

INDICATIONS AND USAGE

Coly-Mycin M Parenteral is indicated for the treatment of acute or chronic infections due to sensitive strains of certain gram-negative bacilli. It is particularly indicated when the infection is caused by sensitive strains of *Pseudomonas aeruginosa*. This antibiotic is not indicated for infections due to *Proteus* or *Neisseria*. Coly-Mycin M Parenteral has proven clinically effective in treatment of infections due to the following gram-negative organisms: *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Coly-Mycin M Parenteral may be used to initiate therapy in serious infections that are suspected to be due to gram-negative organisms and in the treatment of infections due to susceptible gram-negative pathogenic bacilli.

CONTRAINDICATIONS

The use of Coly-Mycin M Parenteral is contraindicated for patients with a history of sensitivity to the drug or any of its components.

WARNINGS

Maximum daily dose should not exceed 5 mg/kg/day (2.3 mg/lb) with normal renal function.

Transient neurological disturbances may occur. These include circumoral paresthesia or numbness, tingling or formication of the extremities, generalized pruritus, vertigo, dizziness, and slurring of speech. For these reasons, patients should be warned not to drive vehicles or use hazardous machinery while on therapy. Reduction of dosage may alleviate symptoms. Therapy need not be discontinued, but such patients should be observed with particular care.

Nephrotoxicity can occur and is probably a dose-dependent effect of colistimethate sodium. These manifestations of nephrotoxicity are reversible following discontinuation of the antibiotic.

Overdosage can result in renal insufficiency, muscle weakness, and apnea (see **OVERDOSAGE** section). See **PRECAUTIONS, Drug Interactions** subsection for use concomitantly with other antibiotics and curariform drugs.

Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnea and neuromuscular blockade following administration of colistimethate sodium. Therefore, it is important to follow recommended dosing guidelines. See **DOSAGE AND ADMINISTRATION** section for use in renal impairment.

Pseudomembranous colitis has been reported with nearly all antimicrobial agents, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

Since Coly-Mycin M Parenteral is eliminated mainly by renal excretion, it should be used with caution when the possibility of impaired renal function exists. The decline in renal function with advanced age should be considered.

When actual renal impairment is present, Coly-Mycin M Parenteral may be used, but the greatest caution should be exercised and the dosage should be reduced in proportion to the extent of the impairment. Administration of amounts of Coly-Mycin M Parenteral in excess of renal excretory capacity will lead to high serum levels and can result in further impairment of renal function, initiating a cycle which, if not recognized, can lead to acute renal insufficiency, renal shutdown, and further concentration of the antibiotic to toxic levels in the body. At this point, interference of nerve transmission at neuromuscular junctions may occur and result in muscle weakness and apnea (see **OVERDOSAGE** section).

Signs indicating the development of impaired renal function include: diminishing urine output, rising BUN and serum creatinine and decreased creatinine clearance. Therapy with Coly-Mycin M Parenteral should be discontinued immediately if signs of impaired renal function occur. However, if it is necessary to reinstate the drug, dosing should be adjusted accordingly after drug plasma levels have fallen (see **DOSAGE AND ADMINISTRATION** section).

Drug Interactions

Certain other antibiotics (aminoglycosides and polymyxin) have also been reported to interfere with the nerve transmission at the neuromuscular junction. Based on this reported activity, they should not be given concomitantly with Coly-Mycin M Parenteral except with the greatest caution.

Curariform muscle relaxants (e.g., tubocurarine) and other drugs, including ether, succinylcholine, gallamine, decamethonium and sodium citrate, potentiate the neuromuscular blocking effect and should be used with extreme caution in patients being treated with Coly-Mycin M Parenteral.

Sodium cephalothin may enhance the nephrotoxicity of Coly-Mycin M Parenteral. The concomitant use of sodium cephalothin and Coly-Mycin M Parenteral should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies and genetic toxicology studies have not been performed with colistimethate sodium. There were no adverse effects on fertility or reproduction in rats at doses of 9.3 mg/kg/day (0.30 times the maximum daily human dose when based on mg/m²).

Pregnancy—Teratogenic Effects

Pregnancy Category C: Colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6% and 2.9% of fetuses, respectively. These doses are 0.25 and 0.55 times the maximum daily human dose based on mg/m². In addition, increased resorption occurred at 9.3 mg/kg. Colistimethate sodium was not teratogenic in rats at 4.15 or 9.3 mg/kg. These doses are 0.13 and 0.30 times the maximum daily human dose based on mg/m². There are no adequate and well-controlled studies in pregnant women. Since colistimethate sodium is transferred across the placental barrier in humans, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether colistimethate sodium is excreted in human breast milk. However, colistin sulphate is excreted in human breast milk. Therefore, caution should be exercised when colistimethate sodium is administered to nursing women.

Geriatric Use

Clinical studies of colistimethate sodium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly

patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pediatric Use

In clinical studies, colistimethate sodium was administered to the pediatric population (neonates, infants, children and adolescents). Although adverse reactions appear to be similar in the adult and pediatric populations, subjective symptoms of toxicity may not be reported by pediatric patients. Close clinical monitoring of pediatric patients is recommended.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: gastrointestinal upset

Nervous System: tingling of extremities and tongue, slurred speech, dizziness, vertigo and paresthesia

Integumentary: generalized itching, urticaria and rash

Body as a Whole: fever

Laboratory Deviations: increased blood urea nitrogen (BUN), elevated creatinine and decreased creatinine clearance

Respiratory System: respiratory distress and apnea

Renal System: nephrotoxicity and decreased urine output

OVERDOSAGE

Overdosage with colistimethate sodium can cause neuromuscular blockade characterized by paresthesia, lethargy, confusion, dizziness, ataxia, nystagmus, disorders of speech and apnea. Respiratory muscle paralysis may lead to apnea, respiratory arrest and death. Overdosage with the drug can also cause acute renal failure, manifested as decreased urine output and increases in serum concentrations of BUN and creatinine.

As in any case of overdose, colistimethate sodium therapy should be discontinued and general supportive measures should be utilized.

It is unknown whether colistimethate sodium can be removed by hemodialysis or peritoneal dialysis in overdose cases.

DOSAGE AND ADMINISTRATION

Important: Coly-Mycin M Parenteral is supplied in vials containing colistimethate sodium equivalent to 150 mg colistin base activity per vial.

Reconstitution: The 150 mg vial should be reconstituted with 2.0 mL Sterile Water for Injection, USP. The reconstituted solution provides colistimethate sodium at a concentration equivalent to 75 mg/mL colistin base activity.

During reconstitution swirl **gently** to avoid frothing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions are observed, the product should not be used.

Dosage

Adults and pediatric patients—Intravenous or Intramuscular

Administration: Coly-Mycin M Parenteral should be given in 2 to 4 divided doses at dose levels of 2.5 to 5 mg/kg per day for patients with normal renal function, depending on the severity of the infection.

In obese individuals, dosage should be based on ideal body weight.

The daily dose should be reduced in the presence of renal impairment. Modifications of dosage in the presence of renal impairment are presented in Table 1.

TABLE 1. Suggested Modification of Dosage Schedules of Coly-Mycin M Parenteral for Adults with Impaired Renal Function

Renal Function	Degree of Impairment			
	Normal	Mild	Moderate	Considerable
Plasma creatinine, mg/100 mL	0.7–1.2	1.3–1.5	1.6–2.5	2.6–4.0
Urea clearance, % of normal	80–100	40–70	25–40	10–25
Dosage				
Unit dose of Coly-Mycin M, mg	100–150	75–115	66–150	100–150
Frequency, times/day	4 to 2	2	2 or 1	every 36 hr
Total daily dose, mg	300	150–230	133–150	100
Approximate daily dose, mg/kg/day	5.0	2.5–3.8	2.5	1.5

Note: The suggested unit dose is 2.5–5 mg/kg; however, the time INTERVAL between injections should be increased in the presence of impaired renal function.

INTRAVENOUS ADMINISTRATION

1. Direct Intermittent Administration—Slowly inject one-half of the total daily dose over a period of 3 to 5 minutes every 12 hours.
2. Continuous Infusion—Slowly inject one-half of the total daily dose over 3 to 5 minutes. Add the remaining half of the total daily dose of Coly-Mycin M Parenteral to one of the following:

- 0.9% NaCl
- 5% dextrose in 0.9% NaCl
- 5% dextrose in water
- 5% dextrose in 0.45% NaCl
- 5% dextrose in 0.225% NaCl
- lactated Ringer's solution
- 10% invert sugar solution

There are not sufficient data to recommend usage of Coly-Mycin M Parenteral with other drugs or other than the above listed infusion solutions.

Administer the second half of the total daily dose by slow intravenous infusion, starting 1 to 2 hours after the initial dose, over the next 22 to 23 hours. In the presence of impaired renal function, reduce the infusion rate depending on the degree of renal impairment.

The choice of intravenous solution and the volume to be employed are dictated by the requirements of fluid and electrolyte management.

Any infusion solution containing colistimethate sodium should be freshly prepared and used for no longer than 24 hours.

HOW SUPPLIED

Coly-Mycin M Parenteral is supplied in vials containing colistimethate sodium (equivalent to 150 mg colistin base activity per vial) as a white to slightly yellow lyophilized cake and is available as one vial per carton (NDC 61570-414-51).

Store between 20°–25°C (68°–77°F). (See USP controlled room temperature.)

Store reconstituted solution in refrigerator 2°–8°C (36°–46°F) or between 20°–25°C (68°–77°F) and use within 7 days.

Rx only.

Prescribing Information as of February 2004.



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